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Proton transport in a binary biomimetic solution revealed by molecular dynamics simulation

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We report the simulation results of the proton transport in a binary mixture of amphiphilic tetramethylurea (TMU) molecules and water. We identify different mechanisms that either facilitate or retard the proton transport. The efficiency of these mechanisms depends on the TMU concentration. The overall picture is more complicated than a recent suggestion that the presence of amphiphilic molecules suppresses the proton mobility by slowing down the reorientation of the surrounding water molecules. It has also been suggested that the hydronium ion induces local water orientational order, which results in an ordered region that has to move along with the proton potentially slowing down the proton transport as suggested by experiment. We find that water-wire like structures formed at low amphiphile concentrations facilitate proton transfer, and reduction of the hydrogen bond connectivity induced at high concentrations retards it. © *2011 American Institute of Physics*. [doi:10.1063/1.3636381]

I. INTRODUCTION

Proton transport is indispensable for many biological reactions and modern technological applications. It plays a crucial role in processes, such as photosynthesis,[1] enzyme catalysis,[2] and fuel cell proton exchange.[3] The proton transport process in aqueous solutions takes place via the Grotthuss mechanism,[4,5] which makes the proton conductivity significantly larger than the ion conductivity.[6] This mechanism involves a proton transfer reaction where a proton hops from a hydronium ion to an adjacent water molecule by interconversion of a hydrogen bond and a covalent bond. In bulk water, the extended hydrogen bond network is important for the efficiency of the proton transport process.[7] When proton transport takes place in a system in which the number of surrounding water molecules is limited, for instance, near the cell membrane surface or amphiphilic molecules, the hydrogen bond network is disturbed. Therefore, the proton transport will strongly depend on the local hydrogen bond network and the local water configurations and dynamics. Our goal is to investigate how proton transport is affected by the local environment and dynamics in a biomimetic mixture of water and tetramethylurea (TMU) molecules that resemble a protein surface with surrounding water molecules.

It has been shown that in binary solutions, the presence of the hydrophobic methyl groups can dramatically reduce the reorientation of the adjacent water molecules and slow down the water rotational dynamics by quenching the "fast (∼100 fs) molecular jumps" of water.[8–10] The water reorientation is regarded as the limiting step for proton transport under confined conditions,[11,12] in contrast to the fast proton hopping mechanism. Therefore, it is tempting to attribute the slow proton mobility in binary solutions to the slow water reorientation retarded by hydrophobic groups.[13] However, it has also been proposed that the reduction of the proton mobility in solutions is caused by microscopic phase separation induced by water clustering at high solute concentrations.[14] To shed light on this issue, simulations at the atomic level are needed. The goal of this paper is to perform such an investigation. Since this, to our knowledge, is the first theoretical attempt to treat this difficult problem, we will discuss the possible caveats, limitations, and possible improvements.

Classical molecular dynamics (MD) does not permit for the simulation of proton transfer. Car-Parrinello molecular dynamics (CPMD) (Ref. 15) allows simulation of proton transfer; however, only picosecond simulations are possible due to the large computational effort needed in such calculations. Therefore, a couple of approximate methods that treat the proton transfer in a classical environment have been developed.[16–20] These methods have already successfully been applied to study proton transport in bulk water,[18,21,22] in protein environments,[23,24] in channels,[16,17] through fuel cell material,[25] and in molecular systems.[26] These methods are of course approximate and they generally treat the proton transfer as a hopping type of motion where recent CPMD simulations have suggested that a more concerted type of transfer is of importance.[27]

In the present paper, we perform MD simulations with the recently developed Q-HOP method[18] to investigate the proton transport process in TMU/H_2O solution at different concentrations. It will give insight into the proton transport in a biomimetic environment and provide the information in the atomic detail, which cannot be obtained directly from experiments.[13] The remainder of the paper is organized as follows. First, we describe the simulation methods in Sec. II. We present the results in Sec. III; then, we discuss their interpretation and relation to previous studies in Sec. IV. Finally, in Sec. V, we will draw our conclusions.

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II. METHODS

The proton transfer was treated with the Q-HOP method[18] implemented in GROMACS 3.3.[28] The Q-HOP MD simulation was proposed by Lill and Helms[18] and was based on quantum mechanically derived proton hopping rates.[18,29,30] In this semi-classical description, proton transfer takes place instantaneously between the donor and acceptor, where the transfer probability (determining the hopping rate) was parameterized with quantum mechanical methods.[29,30] The transfer probability map is based on two parameterized quantities: the donor-acceptor distance (R_{DA}) and the energy difference between the donor-bound state and the acceptor-bound state (E_{12}). The method contains three regimes. If both the R_{DA} and E_{12} are large enough to generate high energy barriers for proton transfer, transition state theory is used for parameterization. If both the R_{DA} and E_{12} are too small to produce energy barriers, the parameterization is based on the numerical solution of the time-dependent Schrödinger equation. Between these two regimes, logarithmic interpolation is used for covering the gap between two separated regions mentioned above. Details on the parameterization are given in Refs. 29 and 30. We reproduced the simulation conditions of Lill and Helms[18] as closely as possible with the exception that we employed the extended simple point charge (SPC/E) force field[31] instead of the simple point charge (SPC) force field for water.

For the MD simulations, we used the force field developed by Belletato *et al.*[32] for the TMU molecules and the SPC/E model[31] for the water molecules. The hydronium ion force field was taken from Lill and Helms.[18] The geometric averages combination rule was used to describe the Lennard-Jones potential parameters between atom pairs. Binary solutions of TMU/water mixture were simulated at nine different concentrations. The mixtures are labeled by the ratio, W, between the number of TMU molecules and the number of water molecules. The compositions and concentration of the simulated mixtures are given in Table I. The simulations were performed in the low acid concentration limit, where each simulation contained one hydronium ion and no counter-ion. We avoided the use of a counter-ion in order to get results that are applicable at low acid concentration.

After a 2 ns equilibrium run for each concentration, the system was assumed to be properly equilibrated. Then, the trajectories were generated in production phase for 10 ns with 20 fs between each snapshot. During the simulation, the SETTLE algorithm[33] was used to constrain bond lengths and angles of water molecules and hydronium ions, and the LINCS algorithm[34] was used for all other bonds and angles, allowing an integration time step of 2 fs. Electrostatic interactions were calculated by the cutoff method instead of Ewald summation, in order to perform simulations without a counter-ion. This is important as we want to simulate the proton transport at low acid concentrations, where the counter-ions do not play an important role. Short-range repulsive and attractive dispersion interactions were described by a Lennard-Jones potential, using 1.5 nm as cutoff length. The temperature of the system was kept constant by the Berendsen coupling method[35] (time constant $\tau = 0.1$ ps) using an external heat bath at 300 K. The pressure of the system was kept constant using the Berendsen coupling method[35] (time constant $\tau = 1$ ps) with a pressure bath at 1 bar.

TABLE I. The composition of the nine different simulated mixtures. All simulation boxes further contain one hydronium ion.

W	TMU	Water
0.00	0	1004
7×10^{-4}	1	1448
0.05	100	2000
0.10	100	1000
0.20	200	1000
0.50	216	432
1.00	216	216
2.00	216	108
5.00	216	43

III. RESULTS

We first calculated the proton diffusion constant in bulk water. This was done by fitting the mean square displacement (MSD) from 0.25 to 25 ps, according to the Einstein relation $\langle r^2 \rangle = 6Dt$, where r is the displacement, D is the diffusion constant, and t is the time interval. We find a proton diffusion constant of $9.0 \pm 0.55 \times 10^{-5}$ cm^2/s in good agreement with previous simulations with the same method,[18] where a value of $9.0 \pm 3.9 \times 10^{-5}$ cm^2/s was found. Both these values agree quite well with the experimentally reported value of 9.3×10^{-5} cm^2/s reported for acids at *p*H 5.5–6.[36] The experimental water diffusion constant is 2.3×10^{-5} cm^2/s and for SPC/E water it was found to be 2.5×10^{-5} cm^2/s.[31] The difference between the proton and the water diffusion shows that significant proton transport via the Grotthuss mechanism takes place. A more recent experimental study using microfluidics reported a proton diffusion constant in the order of 1×10^{-5} cm^2/s for bulk water at *p*H 0–1.[13] This value is even below the normal water diffusion constant indicating that at such low *p*H, collective proton motion and the presence of counter-ions play an important role.

We determined the hydronium ion lifetime, which is defined as the duration that the proton stays on a certain water molecule and is inversely proportional to the proton hopping rate. While the previous Q-HOP study[18] only counted hopping events, where the proton stayed on the acceptor site for longer than 0.5 ps, we counted all hopping events. The proton transfer rates extracted with different experimental/theoretical methods are shown in Table II. The rate of 1.23 ps^{-1} from our simulation is close to the value 1.2 ps^{-1} determined by recent IR experiments,[37] but about twice as fast as the rates obtained by the other methods. When applying the same criteria as Ref. 18, we obtain a proton hopping rate of 0.6 ps^{-1} compared to 0.47 ps^{-1} found in that previous study.

The proton, water, and TMU diffusion constants at different TMU concentrations were calculated in the same way as the proton diffusion constant in bulk. The diffusion constants are given in Fig. 1(a). The proton mobility increases slightly when the TMU concentration increases from W = 0 to W = 0.5. This shows that the presence of the TMU molecules

TABLE II. Proton transfer rates, k_{PT}, in bulk water are given by different experimental or simulation methods.

Method	k_{PT} (ps^{-1})
This work	1.23
NMR	0.67[a]
IR	1.2[b]
Q-HOP	0.47[c]
MS-EVB	0.69[d]

[a]Reference 46.
[b]Reference 37.
[c]Reference 18.
[d]Reference 22.

facilitates proton transport at low TMU concentrations. Then, the proton mobility decreases dramatically as the TMU concentration increases from W = 1 to W = 2. The TMU diffusion is slower than water diffusion below W = 1, and it increases to the same value as the water diffusion at W = 2. The finding that the proton diffusion is optimal at TMU concentrations of W = 0.5 is at odds with the experimental measurements[13] reported at low *p*H, which found a monotonous decrease of the proton diffusion on dilution with TMU. The error bars were obtained by comparing the slope at the first half and the second half of the time interval used to calculate the diffusion constant. The size of the error bars, thus, reflects the nonlinearity of the MSD curves. Using longer time intervals will reduce the error bars. We here chose to match the time intervals used in the original Q-HOP paper.[18] We also calculated the proton diffusion constants using longer time intervals (up to 500 ps) and found no essential difference in the behavior of the obtained diffusion constant. A recent study suggested that the use of a thermostat might affect the diffusion constant leading to diffusion constant that scales proportionally with the thermostat coupling time at low coupling times.[38] We tested that our diffusion constants are robust by varying the thermostat coupling constant. The water and proton MSD's and diffusion constants with different thermostat coupling time constants at W = 0.2 are shown in Figs. 1(b) and 1(c), respectively. We find that the diffusion constant vary by about 10%, when changing the coupling time with a factor 10. The diffusion constant is, thus, essentially independent of the thermostat coupling strength and the MSD is linear after a short initial time period.

The experimental anisotropy measurements of isotope labeled water molecules are essentially determined by the second-order rotational correlation functions of the water O–H bond.[8] Which is defined as

$$R(t) = \frac{1}{2}\langle 3\cos^2(\Theta_{OH}(t)) - 1\rangle, \quad (1)$$

where Θ_{OH} is the angle that the O–H bond has rotated during the time t. These correlation functions obtained at different concentrations are shown in Fig. 1(d). It is seen that the water rotational dynamics is suppressed by the presence of TMU molecules as also found in experimental studies of TMU/water mixtures.[9] The higher the TMU concentration is, the more restricted the water dynamics is. Fitting parameters

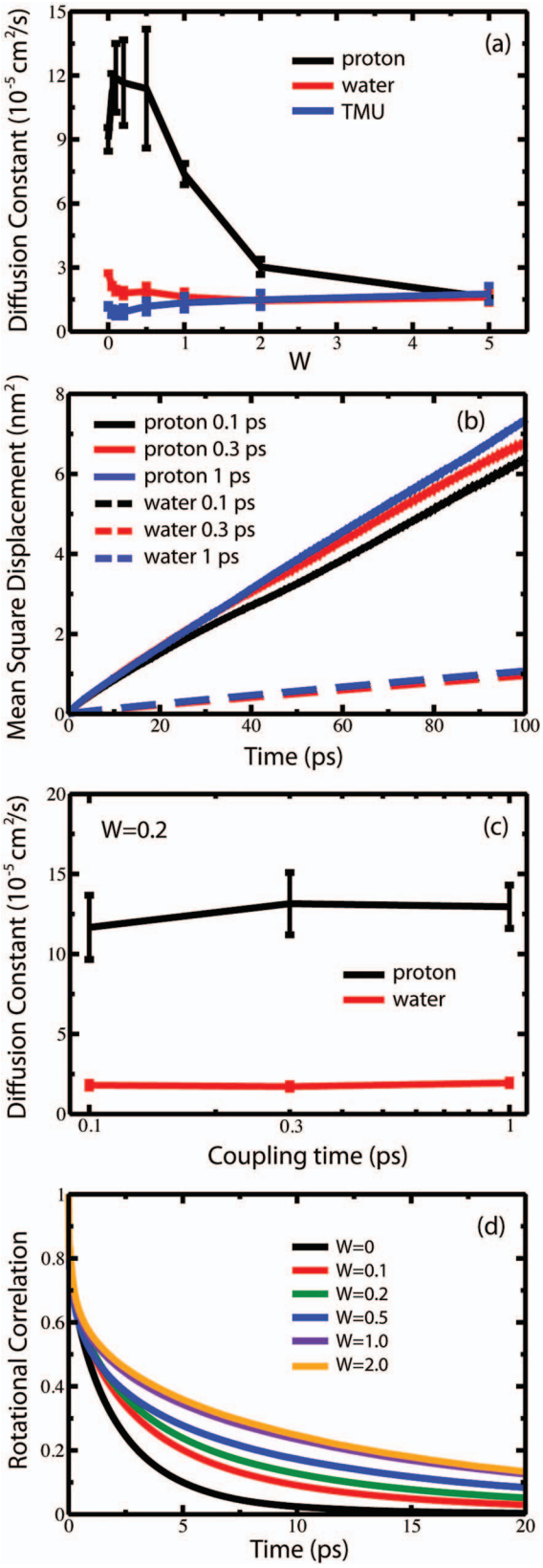

FIG. 1. (a) The diffusion constants of the proton, water, and TMU molecules. (b) The water and proton MSD as a function of the thermostat coupling parameter for W = 0.2. (c) The water and proton diffusion constants (W = 0.2) as functions of thermostat coupling time. (d) The water O–H rotational correlation at different concentrations.

TABLE III. Fitting parameters of the rotational correlation function as shown in Fig. 1(d). The tri-exponential function is chosen as: $A_1 \times \exp(-t/\tau_1) + A_2 \times \exp(-t/\tau_2) + A_3 \times \exp(-t/\tau_3)$.

Concentration	A_1	τ_1	A_2	τ_2	A_3	τ_3
W = 0	0.21	0.13	0.53	1.7	0.19	4.7
W = 0.1	0.24	0.23	0.48	2.9	0.18	12
W = 0.2	0.25	0.27	0.43	3.4	0.20	15
W = 0.5	0.30	0.37	0.36	5.0	0.19	22
W = 1.0	0.27	0.23	0.25	3.6	0.37	19
W = 2.0	0.27	0.25	0.23	3.6	0.40	18

for a tri-exponential fit of the rotational correlation functions are given in Table III.

We examined the number of hydrogen bonds donated from water molecule or hydronium ion hydrogens to TMU carbonyl or water oxygen. For the hydrogen bond criteria, we used a donor-acceptor distance cutoff at 0.35 nm and a hydrogen-donor-acceptor angle cutoff of 30° as commonly used for water.[39] The maximum hydrogen bond donor numbers for a hydronium ion and a water molecule are three and two, respectively, because a hydronium ion has three hydrogen atoms whereas a water molecule has only two. The probability distributions of the hydrogen bond donor number at different concentrations are shown in Fig. 2. The water-TMU and hydronium-TMU hydrogen bond donor number probabilities are similar at the low concentrations (see Figs. 2(a) and 2(b)). At high concentrations, hydronium forms more hydrogen bonds with TMU than water, simply because it is able to form one more bond than water.

When we compare the hydronium-TMU and the hydronium-water hydrogen bond donor number probabilities in Figs. 2(b) and 2(c), we find that the hydronium ion donates two or three hydrogen bonds to water molecules at low concentrations (under W = 0.5), and with very low probability donates a hydrogen bond to TMU. At the highest TMU concentration (W = 5), the hydronium ion predominantly donates three hydrogen bonds to TMU and few to water molecules. This means that the hydronium ion is isolated from water by the presence of TMU at these high concentrations.

We investigated the structure of the hydrogen bond network, when proton transfer takes place, by calculating the hydronium-water hydrogen bond donor number probability at the moment of proton hopping shown in Fig. 2(d) as well as the distribution one would expect to see if the probability of hopping is simply proportional to the number of hydrogen bound with potential acceptor molecules. Indeed, no proton transfer is found, when the hydronium ion is not hydrogen bound with any acceptor molecules. At all concentrations, the proton transfer happens more frequently than predicted assuming that the transfer probability is simply proportional to the number of accessible acceptors, when only one hydrogen bound acceptor is found. The opposite is true for the hydronium ions hydrogen bound with three water molecules. For hydronium ions with two possible acceptors, the real probability for transfer is larger up to W = 0.5 and smaller than predicted for higher concentrations. This means that proton transfer is more likely when there are fewer possible acceptors. Proton transfer from a hydronium ion with just one hydrogen bond donated to water can only lead to proton transport, if a diffusion step is involved as well, otherwise such proton transfer stem is just returning from a dead end. We, thus, find that the two hydrogen bond donor configuration facilitates proton transport more efficiently than the three hydrogen bond donor configuration, which is dominant in

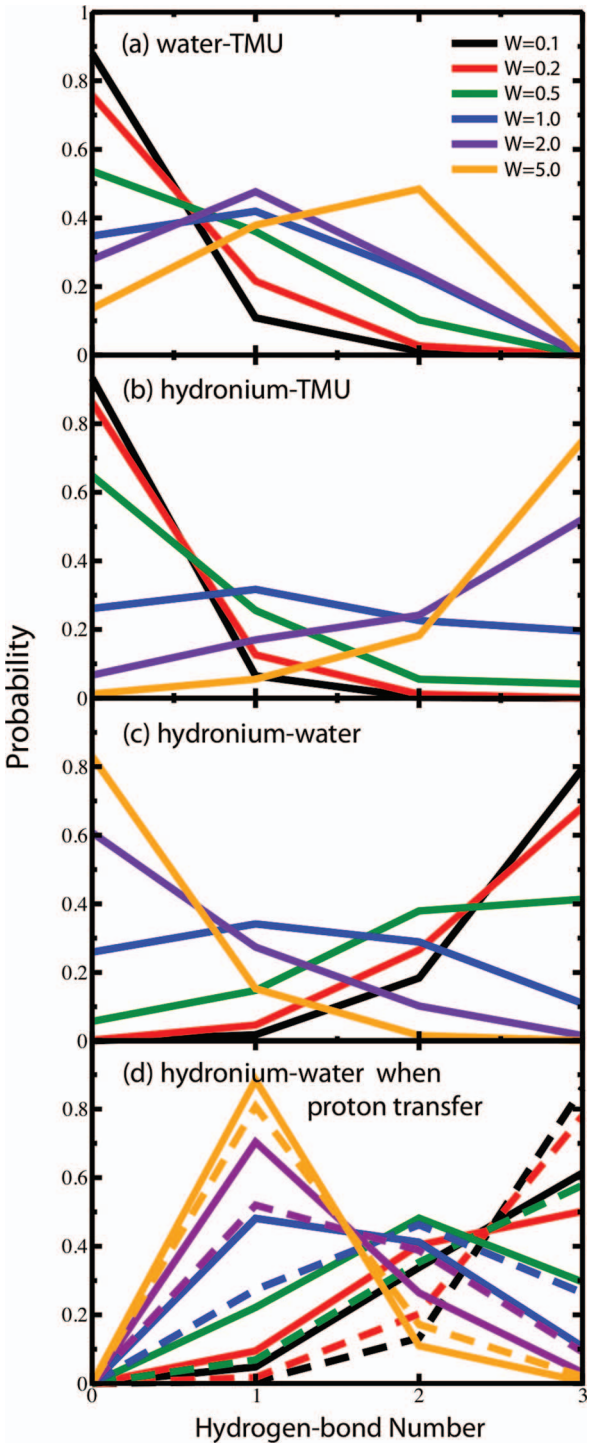

FIG. 2. The probability of hydrogen bond donor number at different concentrations: (a) water-TMU, (b) hydronium-TMU, (c) hydronium-water, and (d) hydronium-water when proton transfer takes place (solid) and the predicted numbers assuming that the transfer probability is equal for each hydrogen bonded proton.

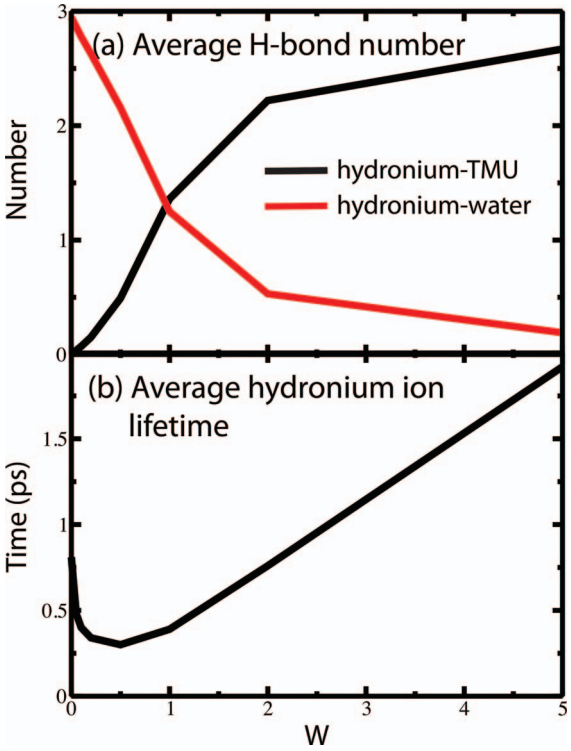

FIG. 3. (a) The average hydrogen bond donor number and (b) the average hydronium ion lifetime as a function of concentration.

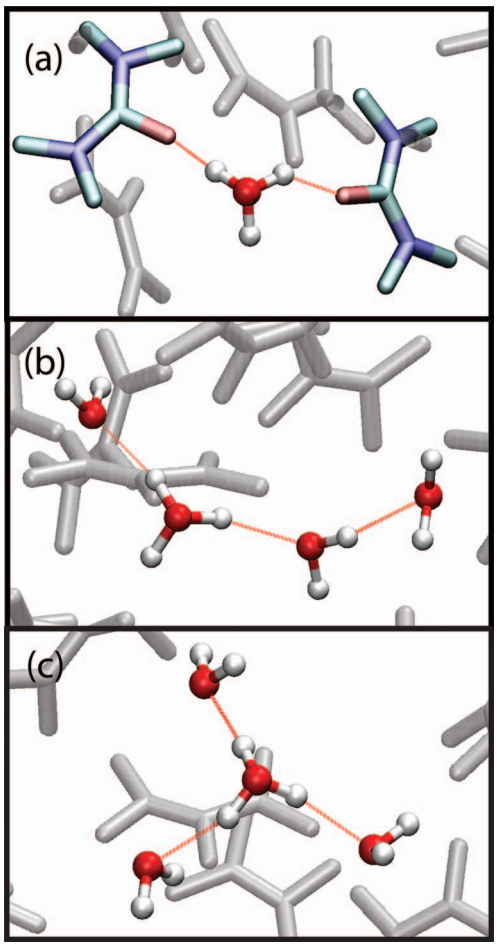

FIG. 4. (a) Illustration of a hydronium ion captured by two TMU molecules, (b) the water-wire like structure around a hydronium ion, and (c) a hydronium ion in a bulk like environment. Hydrogen bonds are shown as red lines.

equilibrium (Fig. 2(c)) at low TMU concentrations. At high concentrations, the proton transfer predominantly takes place in the single hydrogen bond configuration, simply because a hydrogen bond is needed for proton transfer, but this does not lead to transport in itself.

The average hydrogen bond donor numbers (hydronium-TMU and hydronium-water) are shown in Fig. 3(a) as a function of concentration. The hydronium-TMU hydrogen bond donor number increases with increasing TMU concentration, and hydronium-water hydrogen bond donor number behaves in the opposite way. At the lowest TMU concentration (W = 0), the hydronium ion, as a donor, predominantly forms three hydrogen bonds with neighboring water molecules. At the highest TMU concentration (W = 5), on the other hand, the hydronium ion donates two or three hydrogen bonds to TMU molecules, which shows that the hydronium ion is captured by two or three TMU molecules, and the hydronium ion only connects to one neighbor water molecule or even none at all. In such case, proton transport will be determined by the diffusion of the hydronium ion. This configuration is illustrated in Fig. 4(a). At intermediate concentrations as W = 0.5, the hydronium ion predominantly donates two hydrogen bonds to water molecules, which is the building block of the water-wire like structure (Fig. 4(b)).

The average hydronium ion lifetime calculated as a function of concentration is shown in Fig. 3(b). When the TMU concentration is increased from zero, the average hydronium ion lifetime first decreases to the minimum value ~0.3 ps at W = 0.5. When the concentration is further increased, the hydronium ion lifetime increases again. When we compare the average hydronium ion lifetime with the average hydronium-water hydrogen bond number (Figs. 3(a) and 3(b)), the minimum lifetime occurs when there are two hydrogen bonds between the hydronium ion and the surrounding water molecules (see Fig. 4(b)). This again shows that the water-wire like structure enhances the proton transfer between water molecules,[40] whereas the structure of the hydronium ion surrounded by three water molecules (see Fig. 4(c)) creates charge traps along the conduction pathway, which will slow down the transfer process confirming previous observations.[16,17]

To understand the interaction between TMU methyl-methyl groups, water oxygen-oxygen, and hydronium oxygen-water oxygen, we calculate the radial distribution function for these three target groups shown in Fig. 5, and normalize it with the maximum probability of the first peak (the first shell). In the TMU methyl-methyl distribution, three main peaks at distances 0.22, 0.31, and 0.43 nm are observed. They originate from the intra-molecular methyl-methyl connections, which is clear when considering $W = 7 \times 10^{-4}$ (only one TMU molecule in the system). The inter-molecular methyl-methyl distribution is seen at distances interval above 0.33 nm. The higher the TMU concentration is, the higher the probability to find the neighboring methyl groups is. A saturation effect is seen around W = 1. For the water oxygen-oxygen distribution, the location of the first hydration shell

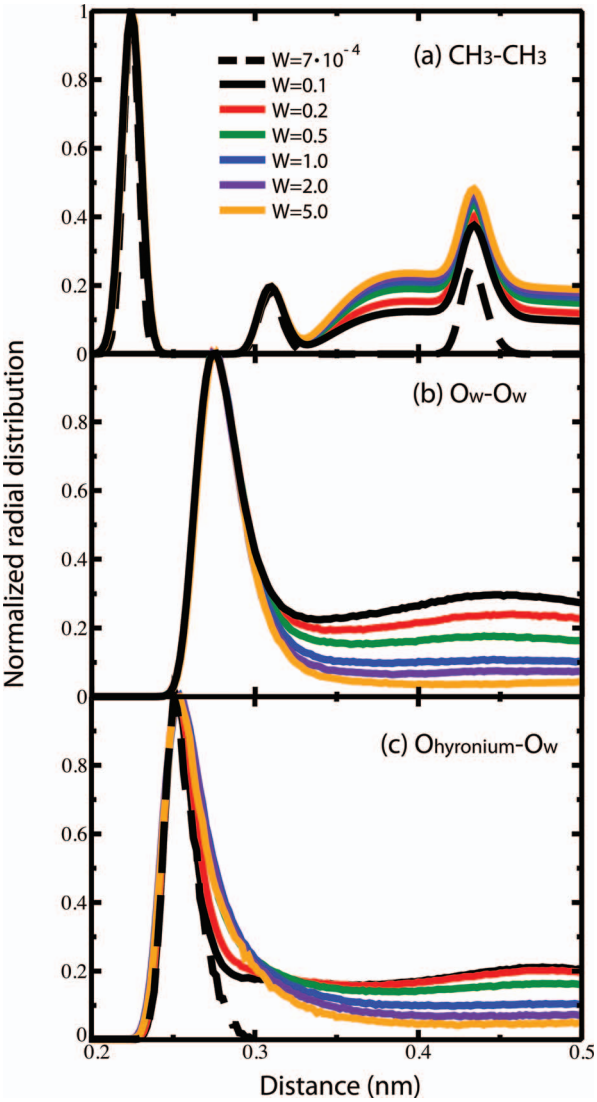

FIG. 5. Normalized radial distribution function of (a) TMU methyl-methyl group, (b) water oxygen-oxygen, and (c) hydronium oxygen-water oxygen. The dashed line represents the distance distribution of R_{DA} when proton transfer takes place in the bulk water.

peaks at 0.28 nm independent of concentration. The second hydration shell located in the interval 0.4–0.5 nm disappears as the TMU concentration is increased. This can only be explained if the water molecules have a tendency to cluster. Such clustering in TMU-water mixtures has previously been reported.[41] For the hydronium oxygen-water oxygen radial distribution (Fig. 5(c)), we find that the distance to the first hydration shell is 0.25 nm, which is shorter than the water oxygen-oxygen distance. This is because the hydronium ion is positively charged dragging the neighboring water oxygens closer. Because the proton transfer probability in the Q-HOP model depends on R_{DA}, we also plot the distribution of R_{DA} at times where proton transfer takes place at W = 0 in Fig. 5(c). We find that the R_{DA} distribution is overlapping with the first shell of the hydronium oxygen-water oxygen distribution. This shows that the proton transfer probability is largely proportional to the probability of finding a certain donor-acceptor distance within the first hydration shell.

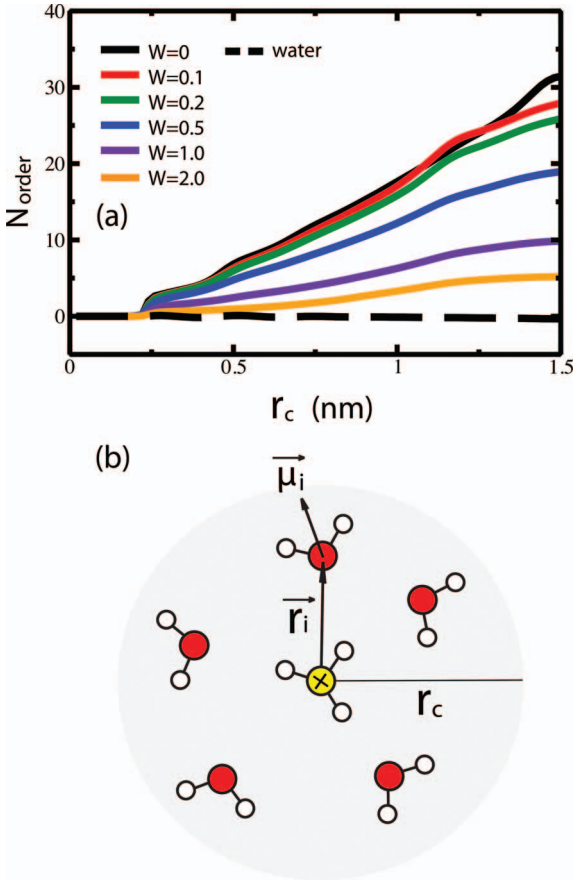

FIG. 6. (a) The orientational order parameter N_{order} (defined in Eq. (2)) as a function of cutoff radius (r_c) at different concentrations. (b) Illustration of the orientation of the surrounding water molecules near a hydronium ion (water oxygens: red circles; hydronium oxygen: yellow circle; hydrogens: white circles).

We investigate the importance of the water molecule orientation near the hydronium ion, by defining an orientational order parameter N_{order}, and calculate it as a function of a cutoff radius (r_c) shown in Fig. 6(a),

$$N_{order}(r_c) = \sum_i \frac{\vec{\mu_i} \cdot \vec{r_i}}{|\vec{\mu_i}||\vec{r_i}|} \qquad (r_i < r_c), \tag{2}$$

where $\vec{\mu_i}$ is the dipole moment of the ith water molecule, and $\vec{r_i}$ is the vector pointing from the hydronium ion oxygen to the ith water oxygen. We only consider the water molecules within the radius r_c. The definition of the orientational order parameter is illustrated in Fig. 6(b). The order parameter at a given radius is determined by the number of the water molecules affected by the hydronium ion charge within the cutoff distance. We define the same order parameter for any other atom simply by replacing the starting point of the $\vec{r_i}$ vector with the position of that other atom. In an isotropic environment, N_{order} should be zero. First, we show that the orientational order parameter around (the oxygen of) a water molecule in bulk water is indeed zero (Fig. 6(a) dashed line). The order around water molecules at different TMU concentrations is also close to zero (not shown).

Around a hydronium ion in bulk water (W = 0), N_{order} is 31 at a cutoff distance of 1.5 nm. Therefore, in bulk water,

TABLE IV. The orientational order parameter around the hydronium ion at different TMU concentrations taken at a cutoff distance of 1.5 nm and the same quantity normalized with the water density.

W	N_{order}(1.5 nm)
0.0	31.4
0.1	27.9
0.2	25.9
0.5	18.9
1.0	9.9
2.0	5.2
5.0	2.6

the water molecules around hydronium are well organized in a relatively short range extending a few solvation shells. At least, the orientation of effectively 31 water molecules are affected by a hydronium ion within 1.5 nm, which is somewhat larger than the number of ordered water molecules (∼19) suggested by experiment at *p*H 0.[7] The simulations prove that a hydronium ion generates a significant ordering of the surrounding water molecules and change their orientation beyond the first solvation shell in agreement with recent terahertz experiments.[7] The values of N_{order} at cutoff distance 1.5 nm at different TMU concentrations are reported in Table IV. At low concentrations, N_{order} is practically unaffected by the presence of the TMU. At high concentrations, N_{order} drops rapidly.

IV. DISCUSSION

In the present simulations, we found a good agreement of the proton diffusion constant in bulk water with that of experiments at *p*H 5.5–6.[36] We noted that the behavior is much different from recent experiments at lower *p*H.[13] The obvious reason for the difference is that at higher acid concentrations (lower *p*H), the interactions between hydronium ions and the interaction with counter-ions start to play a role. In a set of test calculation including a chlorine counter-ion, we indeed found that this strongly affected the proton diffusion. In the present study, we consider the hydronium ions to be independent because there is only one hydronium ion in each simulation box and self-interaction is excluded; however, the orientational order parameter is not fully saturated at distances comparable to half the box length. This means that there might be a slight indirect self-interaction mediated by the orientational ordering of the water molecules. Therefore, the size of the simulation box in our study is at the lower limit of what should be used. One needs to keep this in mind especially when applying higher accuracy methods like CPMD,[15] where one would like to use small simulation boxes to achieve acceptable simulation speeds and typically only the first two solvation shells are included.[27,42,43]

We extracted the diffusion constants using the MSD from 0.25 to 25 ps as was done in the original Q-HOP study.[18] The diffusion in amphiphilic mixtures has been shown to be sub-diffusive at short timescales[41] due to cluster formation. The timescale that we use is on the edge of the region, where true diffusive behavior is found, which might result in slightly overestimated diffusion constants in the present study. We stuck to the procedure used in the Q-HOP study to allow comparison.

We have not investigated the sensitivity to force field parameters. We found the same proton diffusion with SPC/E water as the previous study with SPC;[18] however, these force fields are quite similar and do not explore the wealth of force fields available. A more systematic study of force field parameters would be interesting, and especially the importance of polarizability, as the charged proton can be expected to increase the dipole moment of the surrounding water possibly leading to more order than we observed for the fixed point charge SPC/E model.

In the present simulations, we found that the presence of TMU molecules can facilitate proton transport at low TMU concentrations by reducing the hydrogen bond number (from three to two) between a hydronium ion and adjacent water molecules, and generating water-wire like structures, which is the most efficient configuration for proton transport. This was not observed in experiments performed at higher acid concentrations (*p*H 0–1). This is not a contradiction with the present simulations which were performed to describe the behavior at very low acid concentrations. The proton transport must depend on the *p*H value in solution, and the hydronium-hydronium or hydronium-chlorine interaction probably slows down the proton mobility at high acid concentrations. This is also observed through different proton diffusion constants in experiment at different *p*H values.[37] From the present study, we cannot say anything about the acid concentration dependence. However, we think that the present results can serve as a basis for future studies addressing this issue.

We did not observe water clustering in the present simulations ruling such effects out as important for the proton transport in TMU/water mixtures. Both short and long range water orientations are expected to play a role in the proton transport process. The short range relates to the local hydrogen bond environment, which was already discussed. For the long range, we observed that an average of up to 30 water molecules are oriented by the presence of the hydronium ion and that the general water rotation is monotonically slowed down with increasing TMU concentration. However, the proton diffusion constant increases with increasing TMU concentration at low concentrations. This illustrates that the slow water rotation is not the main factor for the suppressed proton mobility as this would result in a suppressed proton mobility already at low concentrations. Instead, we found that the reduced hydrogen bond network connectivity is the main factor which dominates the proton mobility at the high TMU concentrations. Recent Born-Oppenheimer simulations on small water clusters demonstrated that the proton diffusion constant varies considerably depending on the cluster structure.[44]

The Q-HOP method is known to violate detailed balance.[18] This might have consequences for statistical mechanics properties as the diffusion constant calculated with the method. While in bulk water the proton diffusion constant is close to the experimental value, this might be a result of cancellation of errors. One should be cautious drawing conclusions on the results of Q-HOP simulations, however, the essential observations of this paper, which are the changes in the diffusion constant with variation of the

TMU concentration, should be robust to such errors. Experimental observations and future improved theories should be used to confirm our findings.

V. CONCLUSIONS

In the present work, we performed MD simulations with the Q-HOP method to investigate the proton transport process in a biomimetic TMU/H_2O binary mixture. We examined different phenomena that speed up or slow down the proton transport, when the solute concentration is increased. These are water rotation, orientational order of water around the hydronium ion, water-wire like structure, and hydrogen bond network connectivity. These compete with each other, and dominate the overall proton diffusion at different solute concentration regimes.

The proton diffusion constant first increases with increasing the solute concentration at low concentrations ($W < 0.5$). The water rotation is slowed down by the presence of the amphiphilic molecules, and the water orientational order is almost unchanged. In principle, the slow water rotation retards the proton mobility and the constant water orientational order generates no effect on long range proton transport, which does not match the observed increase in proton transport. The hydrogen bond network connectivity is reduced by the presence of the amphiphilic molecules, resulting in a lower number of possible proton transfer pathways. However, the reduced hydrogen bond connectivity leads to the formation of water-wire like structures, which speeds up the proton transfer between neighboring water molecules. Therefore, in the low concentration regime, the formation of water-wire like structures explains the increase in proton transport observed in the simulations.

The proton diffusion constant decreases with increasing the solute concentration at higher concentrations ($W > 0.5$). The water rotation is even slower than before, but does not change dramatically with increasing the concentration. This is in contrast to the significant decay of the proton diffusion constant from $W = 0.5$ to $W = 5$. The water orientational order is decreasing with amphiphile concentration. This is expected to reduce the energy cost for long range proton transport and, thus, cannot explain the lower proton mobility. The hydrogen bond network connectivity, at these concentrations, is rapidly reduced resulting in breaking of the water-wire like structures and isolation of the hydronium ions. The proton transfer is then blocked by the presence of the amphiphilic molecules. Therefore, at high concentrations, the loss of hydrogen bond network connectivity is essential, and the proton transport becomes dominated by the collective diffusion of water and amphiphile. This finally results in comparable diffusion constants for protons, TMU, and water at $W = 5$.

The same mechanisms identified in the biomimetic mixtures can be expected to play a role in real biological environments. For example, the water-wire like structures are already well known in proton transport protein channels.[45] We can also understand that in order to enhance proton transport in artificial materials, optimizing the order of the water might be the key; so, fewer water molecules need to reorient when protons move around.

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